PRO 542

Drug Class: **Entry and Fusion Inhibitors**

Drug Description

PRO 542 is a novel inhibitor of HIV-1 attachment and entry. PRO 542 is a tetravalent CD4-immunoglobulin (Ig) fusion protein that comprises the D1 and D2 domains of human CD4 genetically fused to the heavy and light chain constant regions of human IgG2. [1]

HIV/AIDS-Related Uses

PRO 542 broadly and potently neutralizes primary HIV-1 isolates in a variety of in vitro, ex vivo, and in vivo preclinical settings. Compared to prior-generation CD4-based proteins, PRO 542 possesses greater valency, size, and conformational flexibility; these structural features may contribute to its enhanced antiviral activity.[2]

PRO 542 has been studied in Phase I trials in HIV infected adults and children. It is currently being investigated for the treatment of HIV in Phase II clinical studies.(2) A multidose, open-label, Phase II clinical study of PRO 542 is currently being conducted in patients with advanced disease who are no longer responding to currently available antiretroviral medications.[3] [4]

Pharmacology

PRO 542 is being developed as an immunotherapeutic and immunoprophylactic for HIV-1 infection. In the therapeutic setting, PRO 542 would neutralize HIV and inhibit dissemination of the virus in vivo, possibly as a combination treatment with other antiviral drugs or biologics. In the immunoprophylactic mode, PRO 542 would be used to neutralize infectious virus and thereby decrease the probability of infection following HIV-1 exposure, in settings such as occupational or perinatal exposure to HIV.[5]

PRO 542 broadly neutralizes primary HIV-1 isolates. PRO 542 binds to the viral surface glycoprotein gp120 and blocks attachment and entry of virus into CD4 cells.[6] CD4-based molecules neutralize HIV by several mechanisms, including competitive inhibition of attachment, dissociation of the exterior envelope glycoprotein (gp120), and inhibition of cell-to-cell transmission of the virus. The incorporation of a human IgG2 heavy chain increases the half-life and minimizes the potential for immunogenicity of the protein.[7]

In a Phase I study of HIV infected adults, evidence of antiviral activity was observed as a reduction in plasma HIV RNA levels when patients were given single intravenous doses of PRO 542 at 0.2 to 10 mg/kg. Area under the concentration-time curve (AUC) and peak serum concentrations (Cmax) increased linearly with dose. The observed terminal serum half-life was 3 to 4 days. No patient developed antibodies to PRO 542.[8]

PRO 542 has been studied in HIV infected children in a Phase I/II study. Dose proportional AUC and Cmax changes were also observed in children. HIV viral load decreased by 80% in four of six children treated with four weekly 10 mg/kg doses. Reductions of viral load were sustained in three children for 14 days after treatment.[9]

In another Phase I study in HIV infected adults with varying degrees of HIV-1 degree progression, patients received single intravenous doses of PRO 542 at 25 mg/kg. Statistically significant acute reductions in HIV-1 viral load were observed across all study patients, and greater antiviral effects were observed in the cohort of patients with more advanced HIV-1 disease. These reductions in viral load continued for 4 to 6 weeks following a single infusion of PRO 542.(2) In this study, Cmax averaged 590 mcg/ml and was typically observed within 2 hours of treatment; the mean serum half-life was 2.9 days. These data are consistent with findings observed previously for doses around 10 mg/kg. For most patients, serum concentrations exceeded the in vitro antiviral amount of drug necessary to inhibit HIV concentration to 50% (IC50) for the patient isolate until approximately 2 weeks post-treatment.[10]

Pharmacokinetics and viral susceptibility of PRO 542 did not vary with disease progression. Antiviral activity could be influenced by the number of CD4 target cells. With fewer cells, the greater distance and time the virus must travel prior to initiating infection may provide a longer window of

PRO 542

Pharmacology (cont.)

opportunity for PRO 542 to neutralize the virus. In the case of PRO 542, viral loads drop within hours of a single administered dose, partially rebound, undergo a secondary decline over a period of days, then remain reduced for up to 6 weeks.[11]

Adverse Events/Toxicity

In previously conducted and currently ongoing clinical trials, PRO 542 has been well tolerated, and no serious side effects have been reported.[12] [13] [14] [15]

Drug and Food Interactions

In vitro, PRO 542 and enfuvirtide are potently synergistic in blocking virus-cell and cell-cell fusion. Synergistic inhibition of virus-cell and cell-cell fusion has been observed for phenotypically diverse viruses over a broad range of drug concentrations.[16]

Clinical Trials

For information on clinical trials that involve PRO 542, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: PRO 542 AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous.[17]

Dosage Form: PRO 542 is prepared as a liquid in phosphate buffered saline (PBS) at a concentration of 5 mg/ml. Vials containing 5 mg, 20 mg, or 100 mg are available for clinical trials.[18]

Storage: PRO 542 should be stored at or below -70 C.[19]

Chemistry

CAS Number: 383198-58-1[20]

Other Names

PRO-542[21]

CD4-IgG2[22]

Further Reading

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Vermeire K, Schols D, Bell TW. CD4 down-modulating compounds with potent anti-HIV activity. Curr Pharm Des. 2004;10(15):1795-803. Review.

Manufacturer Information

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Tarrytown, NY 10591

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help

For More Information (cont.)

Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

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